NDA 20-811/S-002

Allergan, Inc.
Attention: Elizabeth Bancroft
Senior Director, Regulatory Affairs
2525 DuPont Drive
P.O. Box 19534
Irvine, CA 92623-9534

JUL 7 2000

Dear Ms. Bancroft:

PIease refer to your supplemental new drug application dated May 25, 2000, received May 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free,

This supplemental new drug application provides for revisions to the Description, Precautions, and Adverse Reactions sections of the package insert, including the addition of a Geriatric Use subsection.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling of the package insert submitted May 25, 2000, with the following revision, agreed to in our June 29, 2000, telephone conversation:

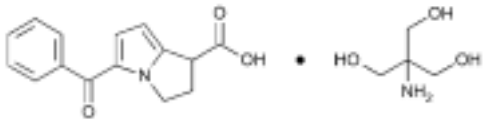
> In the second paragraph of the Adverse Reactions section, the phrase “less than l-10%” will be revised to “approximately 1-l 0%

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-811/S-002.‘” Approval of this submission by FDA is not required before the labeling is used.

ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5%
Preservative-Free
Sterile

DESCRIPTION

ACULAR® PF (ketorolac tromethamine ophthalmic solution) Preservative-Free is a member of the pyrrolo-pyrrole group of nonsteroidal anti-inflammatory drugs (NSAIDs) for ophthalmic use. Ketorolac tromethamine's chemical name is (±)-5-benzoyl-2,3-dihydro-1 *H* pyrrolizine-1-carboxylic acid compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1) and has the following structure:



ACULAR® PF is a racemic mixture of R-(+) and S-(-)-ketorolac tromethamine. Ketorolac tromethamine may exist in three crystal forms. All forms are equally soluble in water. The pKa of ketorolac is 3.5. This white to off-white crystalline substance discolors on prolonged exposure to light. The molecular weight of ketorolac tromethamine is 376.41. The osmolality of ACULAR® PF is 290 mOsmol/kg.

Each ml of ACULAR® PF contains: Active: ketorolac tromethamine 0.5%. Inactives: sodium chloride; hydrochloric acid and/or sodium hydroxide to adjust the pH to 7.4; and purified water.

CLINICAL PHARMACOLOGY

Ketorolac tromethamine is a nonsteroidal anti-inflammatory drug which, when administered systemically, has demonstrated analgesic, anti-inflammatory, and anti-pyretic activity. The mechanism of its action is thought to be due to its ability to inhibit prostaglandin biosynthesis. Ketorolac tromethamine given systemically does not cause pupil constriction.

One drop (0.05 mL) of ketorolac tromethamine (preserved) was instilled into one eye and one drop of vehicle into the other eye TID in 26 normal subjects. Only 5 of 26 subjects had a detectable amount of ketorolac in their plasma (range 10.7 to 22.5 ng/mL) at day 10 during topical ocular treatment. When ketorolac tromethamine 10 mg is administered systemically every 6 hours, peak plasma levels at steady state are around 960 ng/mL.

In two double-masked, multi-centered, parallel-group studies, 340 patients who had undergone incisional refractive surgery received ACULAR® PF or its vehicle QID for up to 3 days. Significant differences favored ACULAR® PF for the treatment of ocular pain and photophobia.

Results from clinical studies indicate that ketorolac tromethamine has no significant effect upon intraocular pressure.

INDICATIONS AND USAGE

ACULAR® PF ophthalmic solution is indicated for the reduction of ocular pain and photophobia following incisional refractive surgery.

CONTRAINDICATIONS

ACULAR® PF is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formulation.

WARNINGS

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other nonsteroidal anti-inflammatory agents. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

With some nonsteroidal anti-inflammatory drugs, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery.

PRECAUTIONS

General: It is recommended that ACULAR® PF be used with caution in surgical patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Wound healing may be delayed with the use of ACULAR® PF.

Information for Patients: ACULAR® PF should not be administered while wearing contact lenses.

The solution from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration. To avoid contamination, do not touch tip of unit-dose vial to eye or any other surface.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Ketorolac tromethamine was not carcinogenic in rats given up to 5 mg/kg/day orally for 24 months (151 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals) nor in mice given 2 mg/kg/day orally for 18 months (60 times the maximum recommended human topical ophthalmic dose, on a mg/kg basis, assuming 100% absorption in humans and animals).

Ketorolac tromethamine was not mutagenic *in vitro* in the Ames assay or in forward mutation assays. Similarly, it did not result in an *in vitro* increase in unscheduled DNA synthesis or an *in vivo* increase in chromosome breakage in mice. However, ketorolac tromethamine did result in an increased incidence in chromcsomal aberrations in Chinese hamster ovary cells.

Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 272 and 484 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals.

Pregnancy:
Teratogenic Effects: Pregnancy Category C. Ketorolac tromethamine, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses up to 109 times and 303 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis assuming 100% absorption in humans and animals. When administered to rats after Day 17 of gestation at oral doses up to 45 times the maximum recommended human topical ophthalmic dose, respectively, on a mg/kg basis, assuming 100% absorption in humans and animals, ketorolac tromethamine resulted in dystocia and increased pup mortality. There are no adequate and well-controlled studies in pregnant women. ACULAR® PF ophthalmic solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects: Because of the known effects of prostaglandin-inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ACULAR® PF during late pregnancy should be avoided.

Nursing Mothers: Caution should be exercised when ACULAR® PF is administered to a nursing woman.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 12 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

The most frequent adverse events reported with the use of ketorolac tromethamine ophthalmic solutions have been transient stinging and burning on instillation. These events were reported by approximately 20% of patients participating in clinical trials.

Other adverse events occurring 1%-10% of the time during treatment with ketorolac tromethamine ophthalmic solutions included ocular irritation, allergic reactions, superficial ocular infections, superficial keratitis, ocular inflammation, corneal edema, and iritis.

Other adverse events reported rarely with the use of ketorolac tromethamine ophthalmic solutions include: eye dryness, corneal infiltrates, corneal ulcer, visual disturbance (blurry vision), and headaches.

DOSAGE AND ADMINISTRATION

The recommended dose of ACULAR® PF Preservative-Free is one drop (0.25 mg) four times a day in the operated eye as needed for pain and photophobia for up to 3 days after incisional

HOW SUPPLIED

ACULAR® PF (ketorolac tromethamine ophthalmic solution) 0.5% Preservative-Free is available as a sterile solution supplied in single-use vials as follows: ACULAR® PF 12 Single-Use Vials 0.4 mL each - NDC 0023-9055-04. Store ACULAR® PF between 15°C-30°C (59°F-86°F) with protection from light.

Rx only

U.S. Patent Nos. 4,089,969; 4,454,151; 5,110,493

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